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Exploring the link between pholcodine exposure and neuromuscular blocking agent anaphylaxis

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Neuromuscular blocking agents (NMBAs) are the most commonly implicated drugs in IgE-mediated anaphylaxis during anaesthesia that can lead to perioperative morbidity and mortality. The rate of NMBA anaphylaxis shows marked geographical variation in patients who have had no known prior exposure to NMBAs, suggesting that there may be external or environmental factors that contribute to the underlying aetiology and pathophysiology of reactions. Substituted ammonium ions are shared among NMBAs and are therefore thought to be the main allergenic determinant of this class of drugs. Substituted ammonium ions are found in a wide variety of chemical structures, including prescription medications, over-the-counter medications and common household chemicals, such as the quaternary ammonium disinfectants. Epidemiological studies have shown parallels in the consumption of pholcodine, a nonprescription antitussive drug which contains a tertiary ammonium ion, and the incidence of NMBA anaphylaxis. This link has prompted the withdrawal of pholcodine in some countries, with an ensuing fall in the observed rate of NMBA anaphylaxis. While such observations are compelling in their suggestion of a relationship between pholcodine exposure and NMBA hypersensitivity, important questions remain regarding the mechanisms by which pholcodine is able to sensitize against NMBAs and whether there are other, as yet unidentified, agents that can elicit similar hypersensitivity reactions. This review aims to explore the evidence linking pholcodine exposure to NMBA hypersensitivity and discuss the implications for our understanding of the pathophysiology of these reactions.

Perioperative anaphylaxis due to neuromuscular blocking agents

Anaphylactic reactions are an important complication during anaesthesia. The severity of reactions can vary, and mortality is estimated to be between 3 and 6% [1]. While there are a variety of structurally distinct drugs and allergens that have been associated with perioperative anaphylaxis, the majority of reactions are accounted for by a relatively small number of agents [2]. Neuromuscular blocking agents (NMBAs) cause the highest number of anaphylactic episodes during anaesthesia, accounting for approximately 60% of reactions [3, 4]. Aminosteroid NMBAs (e.g. pancuronium, rocuronium and vecuronium), benzylisoquinolines (e.g. atracurium and cisatracurium) and succinylcholine (often referred to as suxamethonium) can all elicit anaphylaxis [5]. Figure 1 shows the chemical structure of selected NMBAs. Cross-reactivity between different NMBAs is common, and patterns vary between patients. Skin testing and *in vitro* diagnostic assays can be used to assess which NMBA may be suitable in a patient who has reacted to a drug in this class. Positive skin tests are valuable in confirming allergy to the suspected NMBA with a high specificity and have higher sensitivity than *in vitro* testing for specific IgE to NMBA [6]. In patients with diagnosed NMBA anaphylaxis, cross-reactivity occurs most frequently with suxamethonium and rocuronium [7].

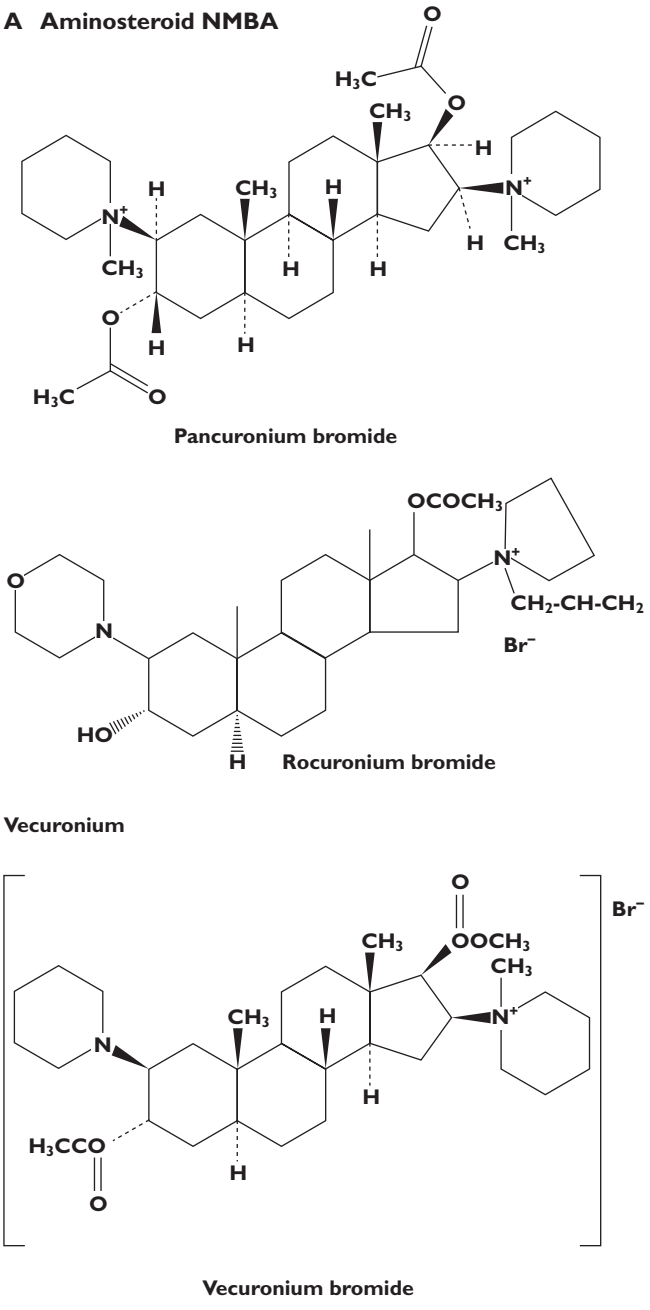


Figure 1

Chemical structure of a selection of neuromuscular blocking agents (NMBAs). (A) Aminosteroid NMBAs. (B) Benzylisoquinoline NMBAs

Epidemiology of NMBA anaphylaxis

Epidemiological studies in this area can be challenging due to difficulties in recording adverse events, standardizing the definition of anaphylaxis and determining the number of anaesthetic procedures where a NMBA was administered in a specific geographical location. Table 1 highlights the variability in reported rates of NMBA anaphylaxis. The incidence of NMBA anaphylaxis varies widely between geographical regions; for example, it accounts for only 11% of anaesthesia-related reactions in the USA compared with approximately 60% in Europe and Australasia [1, 8, 9]. The choice of NMBA during anaesthesia also appears to have a significant impact on the rate of anaphylaxis. While most data relate to the rate of anaphylaxis for rocuronium, a recent Australian study has compared the rate of NMBA anaphylaxis for different agents and demonstrated that the incidence is up to four times higher for rocuronium than for other NMBAs, such as vecuronium [7].

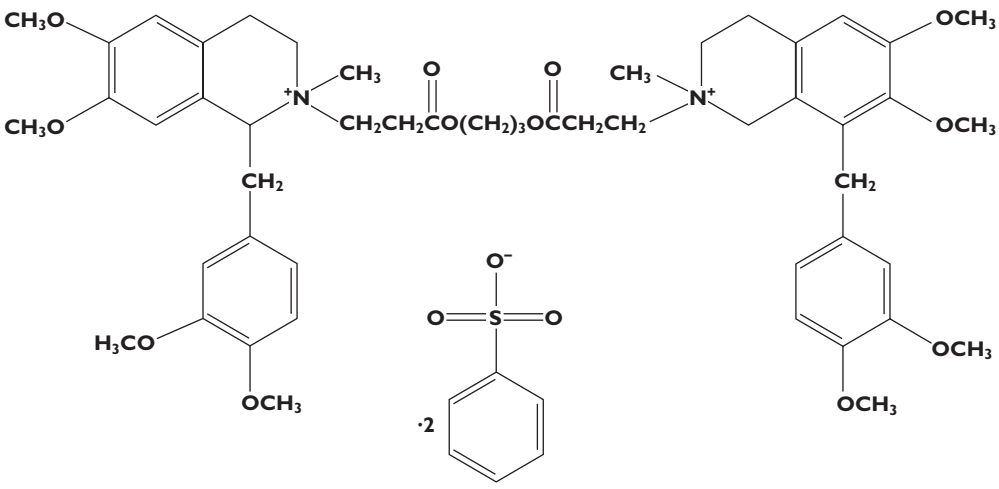
In contrast to many other IgE-mediated drug hypersensitivity reactions to prevalently used drugs, such as penicillin and cephalosporin antimicrobials, a substantial proportion of patients with NMBA anaphylaxis have no history of prior exposure to the drug [10], suggesting that there must be external and geographically variable factors that play a role in sensitizing against NMBAs.

Substituted ammonium ions, pholcodine and NMBA anaphylaxis

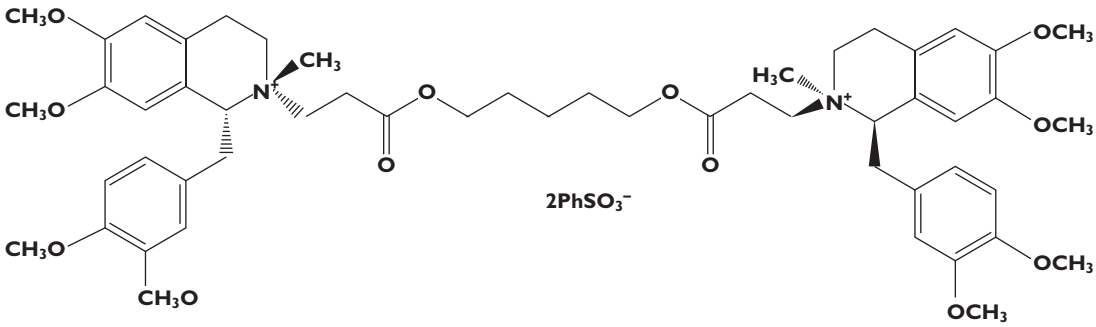
The suggestion of a possible link between NMBA anaphylaxis and cross-sensitizing external factors was first put forward in the early 1980s. Baldo and Fisher identified substituted quaternary ammonium ions as the allergenic determinants of alcuronium, a bis-quaternary NMBA [11]. Using sera from patients with NMBA hypersensitivity, they demonstrated that binding of alcuronium-specific IgE molecules could be inhibited by the addition of a number of compounds that contained quaternary ammonium ions.

This hypothesis was revisited in 2005 upon noting the discrepant rate of NMBA anaphylaxis in some Scandinavian countries. The prevalence of sensitization to suxamethonium, which contains two quaternary amine groups, and morphine, which contains a tertiary amine group, was compared between different categories of patients in Norway and Sweden [12]. Two-thirds of Norwegian patients with NMBA anaphylaxis were sensitized to morphine. Among the morphine-sensitized patients, the level of morphine-specific IgE levels correlated with the level of suxamethonium-specific IgE. Even among Norwegian patients without a history of NMBA anaphylaxis, the rate of morphine sensitization was quite high, with a prevalence of 10% for patients with non-NMBA allergies and 5% for healthy blood donors. In contrast, not a single patient among the Swedish group of allergy patients and blood donors had IgE antibodies against morphine or suxamethonium. As the pattern of sensitization to substituted ammonium ions differed so drastically between neighbouring countries, it was proposed that there must be a contrasting distribution of exposure. The consumption of commonly available compounds containing substituted ammonia groups (in household products and

B Benzylisoquinoline NMBA



Atracurium besylate



Cisatracurium besylate

Figure 1

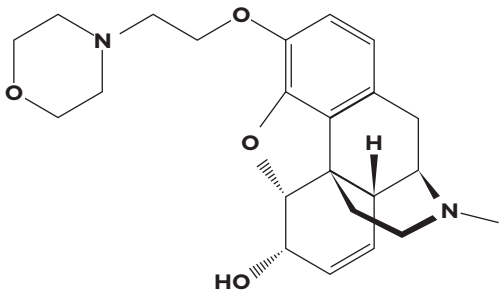
Continued

Table 1

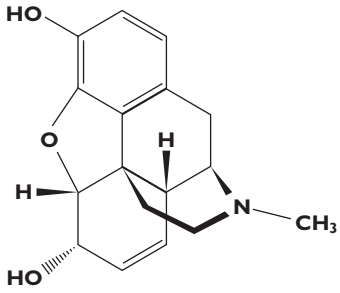
Reported rates of anaesthetic-associated anaphylaxis by country/geographical region

Reference	Year	Country or region	Drug(s)/context	Reported rate of anaphylaxis	Equivalent rate of anaphylaxis (events per 100 000 anaesthetics)
Sadleir *et al*. [7]	2013	Australia	Rocuronium	8 per 100 000 exposures	8 per 100 000
			Atracurium	4 per 100 000	4 per 100 000
			Vecuronium	3 per 100 000	3 per 100 000
Dong *et al*. [9]	2012	France	Anaesthesia	140 per million anaesthetics	
			NMBA	47.4% of reactions during anaesthesia	~6.7 per 100 000
Gurrieri *et al*. [8]	2011	USA	NMBA	Rate not reported; accounted for 11% of reactions during anaesthesia	
Guttormsen [29]	2001	USA	Rocuronium	1 per 1 445 000	0.07 per 100 000
Laake and Rottingen [30]	2001	Scandinavia, excluding Norway	Rocuronium	7 per 800 000	0.88 per 100 000
		Norway	Rocuronium	29 per 150 000	19 per 100 000
Fisher and Baldo [1]	1993	Australia	Anaesthesia	1 per 10 000–20 000	
			NMBA	59% of reactions during anaesthesia	~6 per 100 000

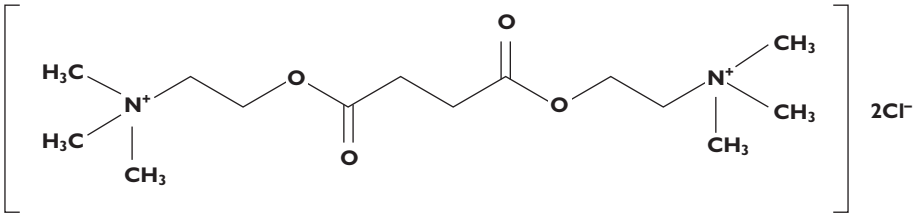
Abbreviation is as follows: NMBA, neuromuscular blocking agent.



Pholcodine



Morphine



Suxamethonium

Figure 2
Chemical structure of pholcodine, morphine and suxamethonium

medications) was compared between Norway and Sweden. Both countries appeared to be exposed to similar compounds, with the one exception being pholcodine, which was not available in Sweden and hence the population exposure was deemed negligible. In contrast, pholcodine was available over the counter in Norway, with an estimated consumption of 42 mg per inhabitant in 2001. This identified pholcodine as the likely culprit for priming NMBA hypersensitivity. Figure 2 shows the chemical structures of morphine, pholcodine and suxamethonium.

Potential sensitizing effect of pholcodine exposure

While many compounds share substituted ammonium ions, it seems that there is something specific to the relationship between pholcodine and NMBA that results in NMBA sensitization and priming of NMBA allergy following pholcodine exposure. Although true pholcodine anaphylaxis is uncommon, we have encountered two patients who had primary allergic reactions to pholcodine, who were subsequently found to have evidence of sensitization to NMBA by skin and serological testing.

The first case is of a 10-year-old girl who presented with an episode of anaphylaxis characterized by facial angioedema, presyncope and gastrointestinal upset 30 min after ingesting a cough syrup containing pholcodine. She subsequently collapsed and lost consciousness for approximately 15 s. She had no prior history of allergy to any other drugs or any foods. She had no history to suggest latex allergy. Skin testing to pholcodine was performed but was uninterpretable as, due to its non-specific histamine release properties, it caused positive responses in four staff members who acted as volunteer

control subjects. However, a more specific indicator, allergen-specific IgE, was positive to pholcodine (6.29 kU l^{-1}; normal <0.35 kU l^{-1}) and to morphine (2.52 kU l^{-1}; normal <0.35 kU l^{-1}) in the child. Skin testing and allergen-specific IgE blood testing was performed to a number of NMBAs to assess potential cross-sensitization. She developed an 8 mm flare reaction upon skin prick testing with neat atracurium. The allergen-specific IgE level to rocuronium was also positive, with a level of 1.01 kU l^{-1} (normal <0.35kU l^{-1}). As a result of this assessment, the patient was advised to avoid pholcodine and also to avoid rocuronium and atracurium if muscle relaxation was deemed essential in future anaesthetics. She had negative skin tests to suxamethonium and vecuronium, which were suggested as suitable alternatives should she require an NMBA in the future.

The second case is of a 65-year-old woman who had anaphylaxis within 30 min of ingesting a pholcodine-containing cough linctus. She had no prior history of NMBA exposure. One week prior to the episode, she had undergone a facetal radiofrequency rhizotomy under sedation. She received hyoscine, fentanyl, alfentanil and granisetron during the procedure. The reaction to pholcodine was characterized by significant upper airway angioedema, presyncope and evidence of hypoxia in the form of confusion. She responded well to treatment with adrenaline. Subsequent testing showed IgE antibodies to pholcodine (4.91 kU l^{-1}; normal <0.35 kU l^{-1}). She also underwent skin testing to NMBA to assess for evidence of cross-reactivity. Skin prick testing, using undiluted drug solutions, was positive for suxamethonium, with a 3 mm wheal and 10 mm flare. She had negative skin prick tests to cisatracurium, pancuronium, rocuronium, vecuronium and atracurium. Intradermal testing, using dilutions of 1:1000 for all NMBAs except atracurium, which was diluted to 1:10 000, was negative except for an 8 mm wheal with suxamethonium. Although allergen-specific IgE to suxamethonium was not detected, on the basis of the higher sensitivity of skin testing, the patient was advised to avoid suxamethonium if a general anaesthetic was needed in the future.

Our case studies illustrate the potential for pholcodine exposure and the development of pholcodine allergen-specific IgE to be associated with sensitivity to NMBA in patients with pholcodine hypersensitivity. This association has been studied extensively by the Scandinavian group, who were alerted by the discrepant rate of NMBA anaphylaxis in Sweden and Norway described previously [12, 9]. In a pilot study, they demonstrated that pholcodine is a potent sensitizer of total serum IgE and pholcodine-, morphine- and suxamethonium-specific IgE in presensitized individuals. In contrast, exposure to other substituted ammonium ion-containing compounds does not result in the same degree of total and pholcodine-, morphine- or suxamthonium-specific IgE sensitization [13].

Following on from these early data, a small, randomized trial was set up to assess the sensitizing actions of pholcodine further [14]. Seventeen patients with a history of NMBA anaphylaxis were randomized to receive a cough syrup containing either pholcodine or guaifenesin. Total IgE and allergen-specific IgE levels were measured before the drug exposure and at 4 and 8 weeks postexposure. While there were significant differences in IgE levels at study baseline, there was a large increase in IgE levels in the pholcodine group but not in the guaifenesin group. The biggest increase in allergen-specific IgE levels relative to baseline was seen with antibodies to suxamethonium, morphine and pholcodine. Interestingly, an increase in allergen-specific IgE levels to seemingly unrelated items, such as inhaled aeroallergens, was also observed for the pholcodine group. Therefore, pholcodine exposure appears to be able to stimulate a broad range of IgE reactivities (at least in the short term). This has been proposed to account for the variation in NMBA anaphylaxis rates between countries but could also conceivably have a broader impact on susceptibility to other allergies.

Effects of pholcodine withdrawal in Norway

Based on the accumulation of data supporting an association between pholcodine exposure and rates of NMBA anaphylaxis, pholcodine was withdrawn from the Norwegian market in March 2007. The effects of removal of pholcodine from the market were studied from a laboratory and clinical perspective by the Scandinavian group [15]. Firstly, the prevalence of allergen-specific IgE antibodies to pholcodine, suxamethonium and morphine in different patient subgroups were analysed prior to pholcodine removal. Among 500 blood donors, the percentage of patients with allergen-specific IgE to morphine, pholcodine and suxamethonium was 5, 6 and 0.4%, respectively, indicating a degree of background sensitization to these drugs within the general population. Three hundred samples from patients tested for suspected allergy but without any specific knowledge of their clinical details were also assessed. Sera from subjects were stratified into subcategories according to their total IgE level. The prevalence of antibodies to pholcodine, morphine and suxamethonium varied according to total IgE level. Among patients with the highest total IgE levels (>5000 kU l^{-1}), the proportion of patients sensitized to pholcodine and suxamethonium prior to the withdrawal of pholcodine was extremely high; 73.5 and 30.6%, respectively.

Analysis of all sera tested for IgE in the 12 months preceding the withdrawal of pholcodine was performed and compared with results obtained in the three consecutive years after pholcodine withdrawal. Data from

Table 2

Number of cases of NMBA-associated anaphylaxis reported to the Norwegian Network for Anaphylaxis during Anaesthesia before and following withdrawal of pholcodine in Norway in March 2007 (adapted from Florvaag *et al*. [15] with permission)

Year	Number of reactions due to NMBA
2005	57
2006	62
2007	56
2008	66
2009	34
2010 (first half)	18

Abbreviation is as follows: NMBA, neuromuscular blocking agent.

approximately 25 000 samples per year was assessed, although reasons for IgE testing and patient demographics in each annual period were not specified. This demonstrated a highly significant decrease in the prevalence of antibodies to pholcodine (11% prewithdrawal *vs.* 5.0, 5.7 and 2.7% for years 1, 2 and 3 postwithdrawal, respectively), suxamethonium (3.7 *vs.* 0.7, 0.3 and 0.3%, respectively) and morphine (10 *vs.* 2.7 and 1.3% for years 2 and 3 postwithdrawal, respectively). Patient total IgE levels also fell following the withdrawal of pholcodine. Among approximately 24 000 samples tested for total IgE, 25.3% had an IgE level >120 kU l^{-1} in 2006, prior to the withdrawal of pholcodine. This fell to 21.5% in 2009, 2 years following the withdrawal of pholcodine. This gives further support to the idea that pholcodine is a potent 'polysensitizer', i.e. that the withdrawal of pholcodine not only led to changes in sensitization to NMBA and pholcodine, but also to changes in total IgE, a nonspecific indicator of atopy.

Clinical reports of NMBA anaphylaxis mirrored the laboratory findings, with a reduction in the number of NMBA anaphylaxis cases reported to the Norwegian network for anaphylaxis under anaesthesia (Table 2).

While these data substantiate the association between pholcodine exposure and NMBA anaphylaxis, there are some limitations and unexplained observations. Firstly, although the rates of sensitization to morphine, pholcodine and suxamethonium fell following the withdrawal of pholcodine, the proportion of patients sensitized to suxamethonium is much lower than that for either morphine or pholcodine. Indeed, among blood donors, only 7% of patients who were sensitized to morphine or pholcodine were also sensitized to suxamethonium. For patients with high total IgE levels, this increases to 37%. Several reasons are suggested for the lack of correlation between morphine/pholcodine and suxamethonium allergen-specific IgE levels. Firstly, the sensitivity of the suxamethonium assay may be lower than for morphine/pholcodine, perhaps due to altered presentation of the putative, shared/cross-reactive epitope. An alternative explanation could be that pholcodine primes NMBA allergy by another mechanism and that the trends in allergen-specific IgE are a secondary phenomenon. Another unexplained observation is the drop in the number of all anaphylaxes and non-NMBA anaphylaxes during anaesthesia from 2005 to 2010; there were 94 anaphylaxes in 2005 (37 non-NMBA related), falling to 53 (19 non-NMBA related) in 2009. A link between pholcodine withdrawal and these data is not immediately apparent and questions the idea of a specific association between pholcodine exposure and NMBA anaphylaxis. The drop in NMBA-related cases of anaphylaxis during anaesthesia has been attributed specifically to the withdrawal of pholcodine. However, another contributory factor could be a change in use of NMBA agents in anaesthesia in recent years. Furthermore, while the changes in allergen-specific IgE and total IgE observed in the study are also attributed to pholcodine withdrawal, this presumes that pholcodine withdrawal is the only environmental variable to have changed during the study. The focus on pholcodine as the only explanation for changing rates of sensitization and NMBA anaphylaxis could potentially overlook other important, as yet unidentified, contributory factors.

Global patterns of pholcodine exposure and NMBA sensitization

The accumulation of data from Sweden and Norway has built a convincing story regarding the role of pholcodine in NMBA anaphylaxis. However, critics of the so-called 'pholcodine hypothesis' have suggested that epidemiological evidence from a relatively small geographical region is not sufficient to prove a causal link between pholcodine exposure and NMBA anaphylaxis. Furthermore, if the link between pholcodine and NMBA anaphylaxis found in Sweden and Norway is interpreted as being causal, significantly more evidence would be needed to prove generalizability across diverse geographical regions. As a result, the Swedish and Norwegian investigators have collaborated with centres in Europe and the USA to expand the analysis of pholcodine and suxamethonium sensitization [16].

The first step of this study involved quantifying pholcodine exposure and consumption. Based on United Nations International Narcotics Control Board database information, pholcodine consumption was determined per million inhabitants. Countries were divided into high- and low-consuming countries accordingly. France, Norway and the UK were high-consuming countries, while Denmark, Finland, The Netherlands, the USA, Germany and Sweden were low pholcodine consumers. Immunoglobulin E antibodies to pholcodine and morphine were significantly higher in the high-consuming

countries. There was no significant difference with respect to IgE antibodies to suxamethonium. However, reanalysis of the data upon excluding The Netherlands and USA did highlight significant differences in the levels of IgE antibodies to pholcodine, morphine and suxamethonium. Such reassessment was undertaken on account of discrepancies between pholcodine consumption data and the prevalence of IgE antibodies to pholcodine. Indeed, there was an unexpectedly high prevalence of antibodies to pholcodine in the USA despite there being no pholcodine-containing drugs available on the US market and no recorded pholcodine consumption. Likewise, while there are no pholcodine-containing drugs available in The Netherlands, there is a surprisingly high rate of pholcodine consumption. It was concluded that the pholcodine consumption data must be interpreted with caution because they do not necessarily equate to population exposure. While this may be true, it casts doubt on whether pholcodine is the only relevant agent in inciting NMBA hypersensitivity and suggests the possibility that there may be other commonly encountered compounds that contribute to cross-sensitization against NMBA and can result in priming clinically meaningful allergy.

This study examined the prevalence of specific IgE antibodies to pholcodine and suxamethonium. Data relating to clinical events (i.e. NMBA anaphylaxis during anaesthesia) were not compared. As discussed previously, analysis of anaphylaxis rates can be challenging and have only been reported for relatively few geographical regions.

Data regarding the use of narcotic drugs worldwide is compiled and updated annually. Table 3 shows data derived from the International Narcotics Control Board's estimates for world requirements of narcotic drugs in 2013 [17]. Pholcodine use continues to vary considerably between countries. Following the withdrawal of pholcodine in 2007, Norway is now among the lowest consuming countries. Countries with high reported rates of NMBA anaphylaxis, such as France and Australia, continue to be among some of the highest consumers of pholcodine. The UK also has high requirements of pholcodine, although the rate of NMBA anaphylaxis in the UK has not been specifically reported.

Table 3

Estimated requirements of pholcodine per million inhabitants for 2013

Rank	Country	Pholcodine (grams)	Population (millions)	Grams per million population
1	Hong Kong	5 000 500	7	714 357
2	Macedonia	150 002	2	75 001
3	Australia	1 550 000	23	67 391
4	Algeria	2 500 000	38	65 789
5	Ireland	300 000	5	60 000
6	France	3 050 000	66	46 212
7	Belgium	230 000	11	20 909
8	Pakistan	2 404 650	183	13 140
9	New Zealand	35 000	4	8 750
10	Malaysia	200 000	30	6 667
11	UK	380 000	63	6 031
12	Bosnia and Herzegovina	24 000	4	6 000
13	Italy	300 000	59	5 085
14	South Africa	240 000	52	4 615
15	Slovenia	9 200	2	4 600
38	Finland	5	5	1
39	Sweden	5	10	0.5
40	Norway	1	5	0.2
41	Denmark	1	6	0.17
42	Romania	1	19	0.05
43	Thailand	1	66	0.02
44	Turkey	1	76	0.01
45	Iran	1	77	0.01
46	Germany	1	82	0.01
47	Brazil	1	194	0.005

The top 15 and lowest 10 countries are shown. Countries with a population of <1 million inhabitants were not included. Data were compiled using International Narcotics Control Board data for 2013 and population estimates [17].

Mechanisms of NMBA sensitization

The comparison of epidemiological data regarding NMBA anaphylaxis rates and pholcodine consumption, together with the serological data pertaining to the prevalence of IgE antibodies against pholcodine and suxamethonium, has been sufficiently convincing to prompt withdrawal of pholcodine in some countries. However, the data also pose important questions about the mechanisms by which pholcodine could incite allergy to related structures, such as NMBA.

The first area of interest relates to the sensitizing capacity of pholcodine and, specifically, how and why are substituted ammonium ions allergenic? It is widely known that opioids can cause direct, non-IgE-mediated degranulation of mast cells. The mechanisms are incompletely understood but would not lead to the production of pholcodine-specific IgE. Morphine-triggered histamine release from mast cells is no longer thought to be due to stimulation of opioid receptors and, indeed, the opiate antagonist naloxone has no effect on the propensity of morphine to release histamine. Current data suggest that opiate-induced mast cell release of histamine involves activation of G-proteins [18–21]. Unlike true anaphylaxis, reactions that involve non-IgE-mediated mast cell degranulation (e.g. due to opiates and vancomycin) appear to be directly related to dose and speed of administration and inversely proportional to the potency of the opiate involved. In contrast, theories of how pholcodine may prime NMBA anaphylaxis relate to IgE-mediated pathways of mast cell activation via (at least in part) shared recognition of substituted ammonium ions. Quaternary ammonium ions are positively charged,

with a NR4+ structure, where R may be an alkyl or an aryl group. Experiments in the 1980s demonstrated that simple di-ammonium salts could provoke histamine release in patients with suxamethonium allergy [22]. The length of the chain linking the ammonium groups appeared to play an important role. When the length between ammonium groups was <4 Å, no histamine release could be achieved, whereas the optimal length for histamine release was ≥6 Å. It was therefore concluded that an optimal length between ammonium ions was needed to permit cross-linking of surface IgE receptors on mast cells in sensitized individuals and hence, histamine release.

Although quaternary ammonium ion allergenicity has been demonstrated, it is not yet clear how a simple polyatomic structure can stimulate IgE responses. In other immediate hypersensitivity models, such as with penicillins, hapten molecules (e.g. proteins, peptides and glycoproteins) drive the allergenic potential of a drug [23]. However, there appears to be no conclusive evidence that conjugation to endogenous proteins to form sensitizing antigenic drug–protein complexes occurs with pholcodine, NMBAs or their metabolites [24]. The possibility that the quaternary ammonium ions are able to bind directly to immune receptors (and specifically IgE on mast cells) and stimulate cellular effector functions is suggested by the aforementioned experiments but has not been definitively proved. This proposed pathogenic mechanism would be analogous to the 'p-i concept' of drug interaction with major-histocompatibility complex molecules and T-cell receptors in delayed/T-cell-mediated hypersensitivity reactions [23]. There is a paucity of information in relationship to the genetic basis of IgE-mediated reactions in general. To date, there are no data regarding genetic associations of NMBA anaphylaxis, such as expression of specific human leukocyte antigen molecules or other immune proteins/receptors.

If it is indeed assumed that the structural cross-reactivity of pholcodine's tertiary ammonium ion with NMBA translates to clinical cross-reactivity and allergy through direct stimulation of immune receptors, then it remains puzzling why exposure to other ammonium ions does not. Likewise, it is unclear why pholcodine does not sensitize against a broader range of ammonium ion-containing substances. It seems that there must be other factors, besides their shared substituted ammonium ion, that contribute to the specific relationship between pholcodine and NMBA allergy. The fact that pholcodine exposure is associated with an increase in total IgE and IgE against seemingly unrelated allergens suggests that pholcodine must have other properties that account for its potent sensitizing effects.

Sensitization occurring through cross-reactivity with environmental factors or another drug is rare; however, cetuximab provides a recently characterized example. Cetuximab is a chimeric antibody that targets the epidermal growth factor receptor and is used in the treatment of cancers, particularly head and neck and colorectal malignancies. It was noted in clinical trials that serious clinical reactions compatible with anaphylaxis appeared to occur significantly more commonly in the South-eastern regions of the USA, with up to 20% of patients experiencing reactions with their first exposure [25]. Of these individuals, 68% were found to have had pretreatment antibodies specific for the oligosaccharide galactose-α-1,3-galactose (α-gal), which is present on the Fab portion of cetuximab's heavy chain.

The source of pre-existing specific α-gal IgE antibodies in patients reacting to cetuximab was not immediately clear. It was noted that there was a striking number of adult patients with anaphylaxis to red meat in South-eastern USA and that these patients also had IgE antibodies to α-gal [26]. This led to a search for a geographically specific factor that could link patients who reacted to cetuximab and those who experienced anaphylaxis after eating red meat. A substantial number of patients who had experienced anaphylaxis to red meat reported a preceding history of tick bites. Indeed, the geographical distribution of the 'Lone Star tick', *Amblyomma americanum*, closely paralleled that of patients reacting to cetuximab and red meat. Prospective serological analysis of samples taken from three patients showed a 20-fold increase in α-gal IgE levels following tick bites. It is therefore proposed that IgE antibodies to *A. americanum* generated following tick bites cross-react with cetuximab (and red meat), resulting in anaphylaxis. In the case of NMBA anaphylaxis, the sensitizing factor resulting in drug hypersensitivity is another drug rather than a vector-borne pathogen, yet the parallels may help to shed light on the pathogenesis of both conditions. Similar concerns have been raised regarding the cross-sensitization to colloidal gelatin intravenous fluids, which also contain α-gal, and patients with allergy to red meat [27].

There are issues that remain unresolved regarding the link between pholcodine and NMBA anaphylaxis. Firstly, the prevalence of antibodies against suxamethonium is relatively low compared with pholcodine or morphine. Secondly, correlation between IgE antibodies against pholcodine *vs.* suxamethonium has not been consistently demonstrated. If one assumes that NMBA anaphylaxis occurs due to IgE antibodies to pholcodine cross-reacting with NMBA *in vivo* to give clinical allergy, why is *in vitro* cross-reactivity not more commonplace? Structurally, pholcodine is an alkyl ether of morphine, formed by replacement of the phenolic hydrogen atom with a morpholinoethyl group (see Figure 2). Although structurally very similar, it is notable that, unlike codeine, pholcodine is not dealkylated to morphine during metabolism nor does it undergo conjugation to glucoronic acid [28]. The effect of these metabolic differences on the ability of pholcodine to sensitize to NMBA is currently unclear. It has also been hypothesized that the tertiary

ammonium group in pholcodine is exposed differently *in vitro vs. in vivo* and that the pathogenic epitope is at least partly dependent on an as yet unidentified carrier [12]. It therefore seems that although the association between pholcodine exposure and NMBA anaphylaxis has been demonstrated, the pathogenic mechanisms connecting these events are yet to be elucidated.

Conclusion

Reactions to NMBAs are the most frequent cause of perioperative anaphylaxis. Although documentation of the epidemiology of NBMA anaphylaxis is incomplete, it is known that the incidence of NMBA anaphylaxis shows considerable geographical variation over ethnically similar regions and this pattern has also changed over time, implying that nonpatient/external factors may contribute to the development of NMBA hypersensitivity. Pholcodine is an antitussive medication available without prescription in many countries. The 'pholcodine hypothesis' proposes that cross-reactivity between substituted ammonium ions found in pholcodine and NMBAs primes IgE-mediated, type 1 allergic reactions to NMBAs. Exposure to pholcodine is associated with increases in IgE antibodies against NMBAs and other allergens. Withdrawal of pholcodine from the Norwegian market has been paralleled by a fall in pholcodine and suxamethonium sensitization rates and also in the incidence of NMBA anaphylaxis. The pathogenic mechanisms by which pholcodine is able to sensitize against other allergens and result in clinically meaningful allergy in the case of NMBAs remain unclear, and there is continued interest in other substances that could cross-sensitize in a similar manner and contribute to perioperative anaphylaxis. More complete study and continued vigilance of the epidemiology of these events and the potential factors driving NMBA anaphylaxis will provide important clues to the roles that pholcodine and other factors have in its pathophysiology.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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